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EXAMINER

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| ART UNIT | PAPER NUMBER |
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| 1644 | 29 |

1644

DATE MAILED: 03/14/01

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

## OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 11/8/00

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☑ Claim(s) 1-18, 31 is/are pending in the application.
Of the above, claim(s) 19-25 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1-18, 26-31 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☐ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

**--SEE OFFICE ACTION ON THE FOLLOWING PAGES--**



★ U.S. GPO: 1996-421-632/40206

## DETAILED ACTION

1. Applicant's amendment, filed 9/2399 (Paper No. 19), is acknowledged.
Claims 1, 3-15, 17 have been amended.
Claims 26-31 have been added.

Claims 19-25 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a nonelected invention.

Claims 1-18, 26-31 are under consideration in the instant application.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Office Action will be in response to applicant's arguments, filed 9/23/99 (Paper No. 19).
The rejections of record can be found in previous Office Actions (Paper Nos. 5/8/13/16).

3. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

4. Claims 1-18, 26-31 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8, 15-26, 33-42 of copending application USSN 08/791,391 essentially for the reasons of record set forth in Paper Nos. 4/8/13/16.
This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's amendment, filed 9/23/99 (Paper No. 19), request that this provisional ground of rejection be deferred until there is an indication of allowable subject matter

Applicant has provided for the common ownership of the instant application with USSN 08/790,540.

5. Claims 1, 2, 9,10, 12-18 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. The specification as originally filed does not provide support for the invention as now claimed: "having greater than 88%/79% identity".

Applicant's amendment, filed 9/23/99 (Paper No. 19), directs support to page 45 for these above-mentioned "limitations".

While the specification as filed provides for 'CL had "88/79%" identity to frameworks 1, 2 and 3 of LM609 heavy chain/light chain; there is insufficient written description for "greater than" as well as "at least one LM609 CDR-grafted heavy/light chain polypeptide comprising a variable region amino acid sequence greater than 88%/79% identity with that shown in Figure 1A/1B" or "functional fragments" thereof, or "nucleic acids" encoding the same; as currently recited..

The specification as filed does not provide sufficient written description for these newly claimed limitations", as they are currently recited. Applicant's reliance on generic disclosure and possibly a single species does not provide sufficient direction and guidance to the "currently claimed limitations". It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it. Also, see MPEP 2163.05 Changes to the Scope of Claims. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office action

Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above.

6. Claims 3-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3-8 are indefinite in the recitation of "or a modification thereof that does not change the encoded amino acid sequence" because its meaning is unclear and ambiguous.

As currently recited, it is redundant of the "nucleotide sequence shown in Figure 1A (SEQ ID NO: 1), for example. If the modification does not change the amino acid sequence, then the modification is the amino acid sequence. Therefore, the "sequence" or "the modification thereof" are the same.

Applicant has relied upon page 17, paragraph 2 of the specification for this recitation, which discloses modifications which do not change the encoded amino acid sequence due to the degeneracy of the genetic codes as well as those which result in only a conservative substitution of the encoded amino acid sequence.

Applicant should amend the claims to recite the nature of the modifications to distinctly claim the intended invention and to distinguish the "modification thereof" from the "sequence" itself.

Applicant should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06

For examination purposes under art; the recitation of 'a modification thereof that does not change the encoded amino acid sequence" reads on modifications which do not change the encoded amino acid sequence due to the degeneracy of the genetic codes as well as those which result in only a conservative substitution of the encoded amino acid sequence.

7. An issue of public use or on sale activity has been raised in this application. In order for the examiner to properly consider patentability of the claimed invention under 35 U.S.C. 102(b), additional information regarding this issue is required as follows:

As pointed out previously, Biotechnology Newswatch (1/16/95 and 2/6/95) disclose the use of LM609 antibody including the humanized version of said antibody. Also it is noted that Cheresh, who developed the LM609 antibody and who conducted the in vivo experiments, is not listed as an inventor.

Applicant's arguments, in conjunction with the Huse declaration and pages of the agreement between Ixsys and Celltech Biologics (Exhibit A) under 37 C.F.R. § 1.132, filed 9/23/99 (Paper No. 19) (and previously filed 12/14/98 in Paper No. 12), have been fully considered but are not found convincing.

It is acknowledged that Huse Declaration and Exhibit A as well as applicant's arguments address the role of Ixsys and Celltech Biologics and confidentiality agreements between these two parties. Upon reconsideration that Ixsys and Celltech Biologics had obligations for the purposes of testing the product; the previous public use or sale activity has been withdrawn with respect to Ixsys and Celltech Biologics.

It is noted that page 33 section 1.1.12 of the agreement was not provided either in this amendment, nor previously in the amendment, filed 12/14/98

It is noted that section 2.2 indicates that the Customer hereby grants Celltech the non-exclusive right to use the Customer materials and the Customer Information for the purpose of the Agreement.

However as pointed out previously; applicant has not set forth restrictions or confidentiality with respect to Scripps as well as the principal investigator Cheresh as it applies to public use and sale; given the evidence that Cheresh as the principal investigator for the scientific team as the Scripps Research Institute (see Biotechnology Newswatch, 1/16/95).

The objective evidence of record was sufficiently informing to the public of humanizing the LM609, encompassed by the claimed invention. Given the absence of factual circumstances surrounding the activity and how these comport with the policies underlying the "on sale" and "public use" bars, the rejection is maintained. See MPEP 2133.03.

Applicant's arguments are not found persuasive.

8. Claims 1-18, 26-31 are rejected under 35 U.S.C. § 102(f) because the applicants did not invent the claimed subject matter.

As pointed out previously; applicant's arguments, in conjunction with the Huse declaration, filed 12/14/98 (Paper No. 11), as well as U.S. Patent No. 5,753,230 (1449) and Biotechnology Newswatch Biotechnology Newswatch (1/16/95) presented an ambiguity with regard to the inventorship of the claimed invention.

Applicant's amendment in conjunction with the Huse declaration under 37 C.F.R. § 1.132, filed 9/23/99 (Paper No. 19), have been fully considered but are not found convincing essentially for the reasons of record.

Applicant maintains that the inventorship has been reviewed and determined to be correct and that both Huse and Glaser have been determined to be inventors of the claimed compositions.

Applicant maintains that Cheresh could be considered, at most, a scientific collaborator but not an inventor of the claimed antibodies and nucleic acids referenced as specifically recited SEQ ID NOS.

However, applicant has not provided sufficient objective evidence or information to address either the contribution of Glaser to the claimed invention, given the Huse Declaration, filed 12/14/98 (Paper No. 12), which indicated that he alone conceived the idea of humanizing $\alpha_v\beta_3$ inhibitory antibodies or the contribution of Cheresh as a scientific collaborator, but not as an inventor.

Again, as pointed out previously, applicant has not provided the facts concerning the nature and role of Cheresh as a collaborator, with respect to humanizing the LM609 antibody. It is noted that Biotechnology Newswatch acknowledges that Cheresh was the principal investigator. It is clear that Cheresh developed the LM609 antibody and that it was possible to determine without undue experimentation antibodies and humanized antibodies having the same properties (see U.S. Patent No. 5,753,230, particularly columns 15-19). Further, U.S. Patent No. 5,753,230 claims the use of LM609 antibody as well as humanized versions thereof. Similarly the instant specification acknowledges that Cheresh developed the LM609 antibody (see pages 7-8, for example) and that generating humanized/CDR-grafted antibodies were known in the art at the time the invention was made (see page 15, for example).

Also as pointed out previously; it was noted that the Huse Declaration indicates that he conceived the idea of humanizing $\alpha_v\beta_3$ inhibitory antibodies. However, it is clear that given U.S. Patent No. 5,753,230 that humanizing $\alpha_v\beta_3$ inhibitory antibodies, including the LM609 antibody was known in the prior art by others.

Also as pointed out previously, given Huse Declaration of sole conception, it is not clear what role coinventor Glaser provided in the claimed invention.

Also as pointed out previously; given that Brooks is an inventor on U.S. Patent No. 5,753,230; it is not clear why he as well as Cheresh are not inventors of the instant invention.

To resolve the ambiguity, applicants may file declarations by the non-applicant(s) Cheresh (and Brooks) disclaiming the invention or a declaration by applicant setting forth the facts which provide an explanation as to why the non-applicant are not inventors. Further, applicant may provide facts why Glaser is an inventor.

Applicant's arguments are not found persuasive.

The arguments of counsel cannot take the place of evidence in the record. In re Schulze 346 F.2d 600, 502; 145 USPQ 716, 718 (CCPA 1965). See MPEP 716.01© for examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration.

9. Upon reconsideration applicant's amended claims, as well as applicant's arguments in conjunction with the Huse declaration under 37 C.F.R. § 1.132, filed 9/23/99 (Paper No. 19), wherein Brooks et al. does not disclose the particular amino acids and nucleic acids encompassed by the claimed invention, which encompasses humanized elements from the LM609 antibody of the prior art but encompasses sequences from other immunoglobulins (for framework residues and residues); the previous rejection as it applies to 1-18, 27-31 under 35 U.S.C. § 102(e) as being anticipated by Brooks et al. (U.S. Patent No. 5,753,230) has been withdrawn.

10. Newly added claim 26 is rejected under 35 U.S.C. § 102(e) as being anticipated by Brooks et al. (U.S. Patent No. 5,753,230) essentially for the reasons of record set forth in Paper No. 16.

Applicant's arguments in conjunction with the Huse declaration under 37 C.F.R. § 1.132, filed 9/23/99 (Paper No. 19) have been fully considered but are not found convincing with respect to newly added claim 26.

Given that claim 26 recites "of a modification thereof or a functional fragments of said LM609 CDR-grafted antibody" and the prior art teaching of humanized LM609 antibodies; applicant's arguments concerning the particular structural characteristics of the claimed limitations are not found persuasive. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed "limitations" read on "modifications thereof or a functional fragments of said LM609 CDR-grafted antibody"

Applicant's arguments are not found persuasive

11. Upon reconsideration of applicant's amended claims and arguments, filed 9/23/99 (Paper No. 19); the previous rejection under 35 U.S.C. § 102(b) as being anticipated by Brooks et al. (Cell, 1994); under 35 U.S.C. § 102(b); as being anticipated by Choi et al. (J. Vasc. Surg., 1994; 1449); and under 35 U.S.C. § 102(a)(e) as being anticipated by Kim et al. (U.S. Patent No. 5,578,704) has been withdrawn in view of deleting the recitation of "substantially the same".

12. Claims 1-18 and 26-31 are rejected under 35 U.S.C. § 103 as being unpatentable over Brooks et al. (U.S. Patent No. 5,753,230; 1449) in view of art known gene cloning and expression strategies for deriving recombinant antibodies and fragments thereof, as disclosed on pages 3-37 or Examples I and II of the instant specification or as cited by references on the 1449 for the reasons of record set forth in Paper No. 16.

The teachings of Brooks et al. in view of art known gene cloning and expression strategies for deriving recombinant antibodies and fragments thereof, as disclosed on pages 10-39 or Examples I and II of the instant specification or as cited by references on the 1449 are of record. Briefly, teach the LM609 antibody as well as humanized forms of this antibody and claim methods of using the LM609 antibody as well as humanized forms of this antibody (see entire document, particularly columns 15-19 and the claims). With respect to specific amino acid changes including those which are "modifications" would be obvious given the teachings of humanized LM609 antibodies and art known methods to generate such humanized antibodies which retain the desired functional characteristics of the native antibody and to alter said antibody for therapeutic uses, including human therapy, as taught and known in the prior art.

Applicant's arguments, filed 9/23/99 (Paper No. 19), have been fully considered but are not found convincing essentially for the reasons of record.

Applicant arguments essentially focus on whether the prior art taught the structural features of the LM609 antibody, particularly the nucleic acid or amino acid sequences of the LM609 antibody.

As pointed out previously; the amino acid and nucleic acid sequences associated with the LM609 antibody including those of humanized LM609 antibodies would have been available to the ordinary artisan, given the availability of the LM609 antibody and hybridoma together with general immunoglobulin gene cloning and expression strategies. It would have been have been a matter of routine experimentation well within the ordinary skill level of art to generate chimeric or humanized LM609 antibodies, DNA encoding said antibodies. Given the highly conserved nature of immunoglobulin gene organization and structure and the availability of probes and PCR primers for immunoglobulin gene cloning, one of ordinary skill in the art could have isolated the functionally rearranged heavy and light chain variable regions from the LM609 hybridoma cell line and determined their sequences with a complete expectation of success. For example, the ordinary artisan does not need to determine the amino acid sequences of a rearranged V (variable) region before cloning. The claims do not differ unexpectedly or unobviously from what one of ordinary skill in the art would have expected to obtain given the known LM609 hybridoma thereof, the known heavy and light chain and the art known techniques regarding the production of chimeric antibodies, as acknowledged by the number of available art known procedures disclosed in the instant specification and cited on the Information Disclosure Statement. The claimed DNA sequences must encode a recombinant antibody comprising heavy and/or light chain variable regions of the LM609 antibody.

Immunoglobulin gene structure and organization were well understood in the art a the time the claimed invention was made and that strategies for cloning the DNAs encoding immunoglobulin variable regions genes were well established in the art at the time the claimed invention was made, as were methods for the production of DNA constructs encoding immunoglobulin variable regions. In addition, it was known at the time the invention was made that the benefits of producing recombinant antibodies to reduce the immunogenicity of therapeutic and diagnostic antibodies in human patients. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

As pointed out in the previous Office Actions, it was noted that the instant disclosure relied upon standard humanization procedures to derive the claimed antibody and nucleic acid compositions. Also, it was noted that Biotechnology Newswatch (1/16/95 and 2/6/95) references above support the routine nature of providing an antibody/hybridoma of interest to a commercial interest to develop humanized antibodies and the nucleic acids encoding said antibodies by routineers in the art at the time the invention was made.

Applicant argues that the claims recite structural characteristics which are not taught or suggested in any of the cited references. Applicant argues that Brooks et al. does not teach or suggest the claimed human acceptor framework sequences LM609 CDR's, encompassed by the claimed SEQ ID NOS:.

Applicant argues in conjunction with Deuel that the prior art, including Brooks et al. does not teach nor suggest the nucleic acids having the structural characteristics of the specifically recited SEQ ID NOS.

Applicant argues that the prior art describes the mouse antibody and not applicant's claimed non-mouse antibodies having human acceptor framework sequences with LM609 CDR's

In contrast to applicant's assertions and for the reasons of record and reiterated above; the claimed antibodies and nucleic acids do not differ unexpectedly or unobviously from what one of ordinary skill in the art would have expected given the availability of the LM609 antibody and hybridoma in the prior art as well as the art known techniques regarding the production of chimeric and humanized antibodies at the time the invention was made, as acknowledged by the number of available art known procedures disclosed in the instant specification and cited on the Information Disclosure Statement.

For example, page 15, paragraph 1 of the specification discloses that functional replacement of the CDRs was performed by recombinant methods known to those skilled in the art, commonly referred to as CDR grafting. Also, page 20, paragraph 1 of the specification discloses that identification of amino acids to be changed can be accomplished by those skilled in the art using current information available regarding the structure and function of antibodies as well available and current information encompassing methods for CDR grafting procedures. In addition, page 20, paragraph 2 of the specification discloses using the above described methods known within the art, any or all of the non-identical amino acids can be changed either alone or in combination with amino acids at different positions to incorporate the desired number of amino acid substitutions at each of the desired positions. Page 21, paragraph 1 discloses that the functional replacement of amino acids is beneficial when producing grafted antibodies having human framework sequences since it allows for the rapid identification of equivalent amino acid residues without the need for structural information or the laborious procedures necessary to assess and identify which amino acid residues should be considered for substitution in order to successfully transfer binding function from the donor. Also see (Singer et al., J. Immunol. 150: 2844-2857, 1993 and Padlan, Mol. Immunol 28: 489-498, 1991 of the Information Disclosure Statement; which provide for art known procedures and expectation of success in humanizing known antibodies of interest, including deriving the appropriate changes to derive the desired reduction in reduced immunogenicity and in desired specificity. The claimed grafted antibodies and associated nucleic acids were predictable by the known and practiced means (e.g. computer modeling) at the time the invention was made. It is noted that Padlan discloses the same procedures using the same frameworks in procedures for reducing the immunogenicity of antibody variable domains while preserving their ligand-binding properties as relied upon in applicant's claimed invention (see entire document).

Therefore, it appears that applicant has relied upon the same starting material as the prior art (LM609 antibody and hybridoma) and that applicant has relied upon the same recombinant means to derive the same antibodies and nucleic acids derived from humanizing the LM609 antibody taught and claimed by the prior art. It is clear that Brooks et al. teach antibodies that have the same or similar immunoreactive characteristics and compete for binding to the same preselected target molecule as the LM609 antibody (see columns 15-18, particularly column 17). In contrast to applicant's assertions; humanizing the LM609 antibody or modifying humanized LM609 antibody and its associated nucleic acids in achieving the claimed limitations was known and obvious, given the same starting materials, including the LM609 antibody/hybridoma and acceptor molecules and given the same recombinant means to achieve the same humanized antibodies as clearly taught and known in the prior art. As pointed out above, the modifications other than simple CDR-grafted LM609 antibody appear to be predictable or to be predicated on the same standard and known computer modeling in the prior art in humanizing antibodies of interest.

Also as pointed out above, for examination purposes under art; the recitation of 'a modification thereof that does not change the encoded amino acid sequence" reads on modifications which do not change the encoded amino acid sequence due to the degeneracy of the genetic codes as well as those which result in only a conservative substitution of the encoded amino acid sequence. Such modifications would have resulted in humanized LM609-specific antibodies encompassed by the claimed invention.

Also, the claims recited functional fragments thereof and again; such limitations would have been obvious in view of the prior art teaching of generating humanized LM609-specific antibodies.

Applicant's arguments are not found persuasive.

13. No claim is allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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December 1, 1999
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